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Fresh approaches to vaccine development

New financial and economic models are required to bring more vaccines against a wider range of diseases to the market

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Vaccines have been medicine's most powerful tools in the fight against infectious diseases. They helped to eradicate smallpox and polio (nearly) and dramatically reduced the toll of measles, meningitis, yellow fever, human papillomavirus, mumps, rubella and other diseases. Recent advances have also enabled novel platform technologies that could greatly speed up the development of new vaccines against a plethora of pathogens. And yet, bewilderingly, the number of new vaccines being approved has been steadily decreasing. While some pathogens, such as HIV, malaria and tuberculosis, are notorious for being able to evade vaccine candidates, for many others, it is not down to difficult science, but simple economics. The costs, time and uncertainties of development, clinical testing and production provide a strong deterrence to the small number of pharmaceutical companies that have the infrastructure, know-how and money to develop and produce vaccines.

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This problem became painfully acute during the 2013–2016 Ebola outbreak, and prompted leading experts from policy, academia and industry to call for urgent reforms to the vaccine production system and better ways of licensing vaccines that are not primarily attractive for pharmaceutical companies. "We need to develop institutional momentum for developing vaccines as a public good", commented Kendall Hoyt, assistant professor at the Geisel School of Medicine at Dartmouth College. "Not all vaccines can be developed as a commodity; there are times when the market just fails".

Beyond Ebola

The Ebola virus outbreak that began in late 2013 in southern Guinea exposed how unprepared the world is for a new epidemic (Fig 1). The initial response was ravaged by misdiagnoses, failing health systems and a lack of national and international leadership. Within months, the virus spread out into the wider West African region. There were no approved drugs to treat patients and no vaccines to protect frontline health workers and the population in the area. By the time the outbreak subsided, more than 28,000 people had been infected and more than 11,000 had died, despite dedicated research efforts into a vaccine against the virus since the turn of the millennium. "It's a dilemma", said Thomas Geisbert, a Professor at the Department of Microbiology and Immunology at the University of Texas Medical Branch. "You have an agent that does not occur very often. When it does pop up, it is very sad for the those impacted by it, but it is not very large. Then something like the Ebola outbreak in West Africa happens and you are blown away. Who is going to pay? We do not have the financial incentive for a lot of companies to develop a vaccine from this research, unless it is just doing the right thing".

It is not just the lack of financial incentives for companies that hold back vaccine development: societal factors play an important role, too. "We, as a society, are reactive by nature", said Rino Rappuoli, Head of External Research and Development at GSK Vaccines. "You can think of vaccines as a kind of life insurance; there is an incredible social value. Yet while we put huge amounts of money into curing people who are sick, relatively little attention is paid towards keeping people healthy".

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Yet, the Ebola epidemic did prompt funding agencies, academia and industry to accelerate vaccine development in a manner unseen in previous epidemics. But as one of the vaccines completed clinical trials in Guinea in 2015 [1], they had to face up to the harrowing irony that a candidate vaccine had already been shown to be effective in macaque monkeys more than a decade earlier [2]. It could have been developed into an efficient vaccine for humans; instead, it just sat there. "At the time, there was no interest from large global companies in making an Ebola vaccine", explained Geisbert, who co-led the study while working at the United States Army Medical Research Institute of Infectious Diseases. "It was not like you were making a drug that was going to cure cancer, heart disease or even influenza. It was really frustrating".

That a candidate vaccine existed for Ebola at all was down to investments made by several governments in the early 2000s in response to concerns that it could be used as

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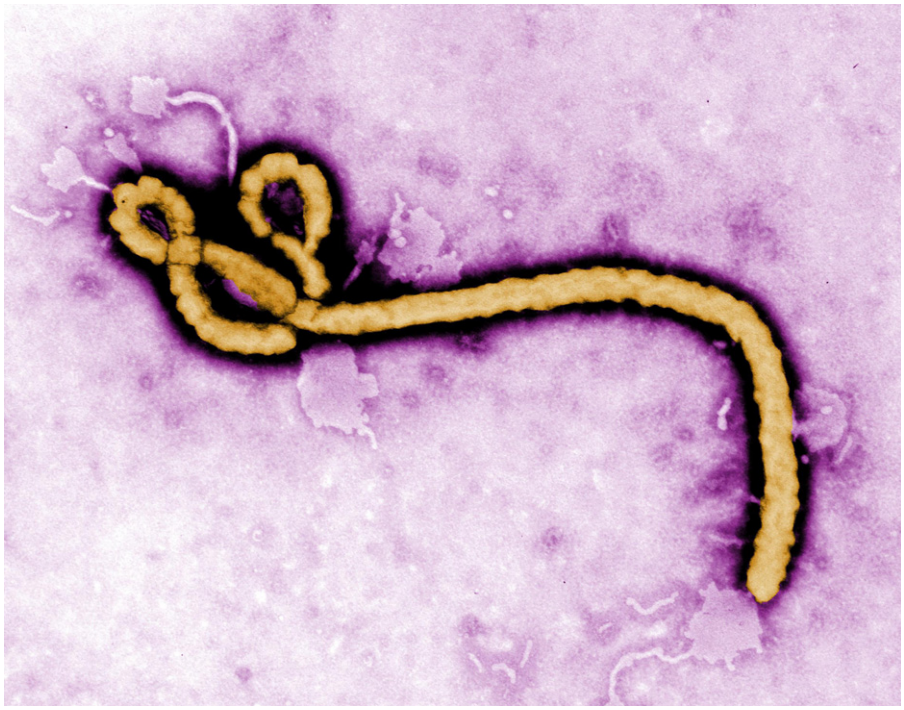

Figure 1. Transmission electron micrograph image of an Ebola virus virion.
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a biological weapon. But analysts warn that it is unlikely that such a convenient pipeline of candidates will be available when the next infectious pathogen breaks out [3]. Thousands of disease outbreaks occur each year around the world, many of which have the potential to turn into epidemics in the light of growing populations, habitat encroachment, and globalised trade and travel networks. "There was complacency all the way around, I don't think people were prepared", Geisbert says. "West Africa taught us a lesson: that in the right circumstances, in resource poor countries, circumstances can get out of control".

A major problem is that investments in new vaccines are nearly not enough. Corporate expenditure on vaccine research is geared towards developing vaccines against diseases that affect affluent countries [4]. A long list of vaccine candidates for many diseases are left in limbo in various stages of development, including diseases that plague low-resource countries, such as Leishmaniasis, Chikungunya and Shigella, or others that have recently come on to the radar as a global health threat, such as Zika virus, Nipah virus and Middle East respiratory syndrome (MERS). Even successfully tested vaccines do not necessarily make it to the market owing to financial and economic factors. GSK, for instance, successfully tested a new vaccine against hepatitis E in collaboration with the United States Army in a phase II trial in Nepal, but the company had already decided before the trial that it would not seek market authorisation for economic reasons. An approved vaccine for a strain of Lyme disease was licensed in 1998, only to be pulled from production when demand dropped in the wake of negative media coverage and fears of side-effects.

Market failure

Taking a vaccine candidate from beginning to end is an enormous endeavour that can take up to 15 years and reach costs nearing €1 billion. Add time-limited patent protections juxtaposed against time-draining regulatory approval, and it takes an audacious executive to take a chance, unless there is some clear return of investment. Understandably, pharmaceutical companies prefer to work on vaccines that mostly affect affluent countries, where public health systems are more likely to eventually cover the costs. "In the past, pharmaceutical companies have picked up one or two promising candidates to show good will—GSK did this with malaria and several companies did this with Ebola", Rappuoli explained. "Right now, it is widely assumed that pharmaceutical companies will continue to provide a solution. The industry has the know-how to translate science into products. But it cannot be the job of companies alone to provide vaccines if there is no market for the product. In addition to our social responsibilities, pharmaceutical companies must make a profit. There is now a huge gap and no one is filling this gap. Pharma, biotech, charities, foundations and government need to get together to discuss these issues and ask: if we want to have a global health agenda, what is the role of companies, foundations, and government in vaccine development for neglected infectious diseases?" Organisations such as the Wellcome Trust, the Bill and Melinda Gates Foundation or the Drugs for Neglected Diseases initiative already make crucial contributions to vaccine development and access. But it will take more to develop vaccines against the huge range of diseases, known and unknown, that impact lives and livelihoods the world over.

Build governance and coordination of funding

This realisation has led to a number of calls for collective funding to address the issues. One proposal is a multi-billion dollar global fund to tackle the interrelated challenges of emerging infectious diseases, neglected diseases and antimicrobial resistance [5]. Another calls for a fund to develop vaccines against emerging epidemic infections [6]. At the heart of these proposals is the ambition to strengthen links between industry, civil society and foundations, promote collaboration, agree on priority diseases and facilitate core principles of open innovation at the global level.

Crucially, while the eyes of the world were on West Africa, proponents had grasped the opportunity to launch the Coalition for Epidemic Preparedness Innovations (CEPI). The governments of Norway and India, together with the Wellcome Trust, and the Bill and Melinda Gates Foundation pooled an initial $460 million into an independent body that supports projects to develop vaccines for high-risk diseases. More governments have since joined the initiative, which aims to develop vaccine candidates through to stage IIb clinical trials, beginning with three priority diseases: Lassa

fever, Nipah virus infection and MERS. "The Ebola crisis was a huge tragedy, but it also demonstrated that it is possible to do clinical testing and development during an outbreak", commented John-Arne Røttingen, Chief Executive of the Norwegian Research Council and adjunct professor at the Harvard T.H. Chan School of Public Health, who was also the founding interim CEO of CEPI. "Without a clear problem and a solution and without the high political interest that the outbreak caused then, there would have been no chance to mobilise CEPI. It came on the G7, G20, UN General Assembly, and World Health Assembly agendas and is now one of the major issues in global health".

While CEPI's financial backing is still less than what would be needed to take even a single vaccine against preventable diseases from the beginning to the end of development, that is not the point. CEPI is rather a component of what many experts hope will be a major shakeup of the way in which vaccines are funded, developed and delivered. For Røttingen, this is as much about fighting time and cost as is it is about fighting disease. "We made two types of strategic goal", he said. "Firstly to develop specific vaccine candidates to be taken forward to phase II development for specific priority diseases. Secondly we want to develop adaptive platforms that will enable us to quickly take information on a new pathogen and integrate that on a vaccine platform".

New technologies

In fact, researchers have developed a number of techniques and technology platforms that could have a major impact on production and distribution. One goal is the development of modular platforms to develop vaccines more quickly and cheaply. Most vaccine development has used weakened or inactivated viruses to trigger an immune response. New technologies such as mRNA vaccines use information from viral genome sequencing which, rather than prepping your body's immune system with molecules resembling those in a pathogen, encourages a person's own cells to make the components needed to provide a vaccine. In theory, it could create a scaffold that can be adapted to other viruses, especially those in the same virus family. Using such methods, scientists working for the US National Institutes of Health developed a promising DNA vaccine candidate for Zika virus based on a platform previously used to develop a candidate vaccine against West Nile virus.

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These technologies could enable researchers to identify antigenic parts of a new virus based on their genome sequence and insert them into a new construct to quickly produce a vaccine candidate for testing. In theory, it could also allow researchers to quickly generate and test a vaccine against a new pathogen that has not been seen before. "There is great scope for developing potential vaccines using those platforms", said Stanley Plotkin, Emeritus Professor of Pediatrics at the University of Pennsylvania. "We have to be honest and point out that we do not yet have a licensed DNA or RNA vaccine for humans, and vectored vaccines are relatively few, but I think there is no doubt that they are very promising".

A new generation of vaccines also presents a tantalising opportunity to speed up and improve the production process. DNA and RNA vaccines in particular could be produced at lower cost, opening up the possibility to make vaccines at the doorstep of potential epidemic hotspots. Getting to this stage is still a way off and will require strategic investment in production and innovation in developing countries with a high risk of epidemics. "We are seeing an increasing sophistication of developing country manufacturers", Plotkin commented. "Up until recently, they were capable of producing vaccines for developing countries but doing little R&D. That is changing and those companies in particular in India, China and Brazil will be important contributors in the future".

Developing a conducive environment

More immediately, experts have urged the development of new market incentives. "We have underinvested in vaccine platform technologies", said Hoyt. "They are a longer term, higher risk investment and often lose out to other investments in private sector R&D portfolios. We need to try to realign resources to meet larger public health needs. It is about improving speed, a duty-driven ethos of vaccine development and creating the institutional environment that would permit and sustain it and ensure that vaccines do not fail for reasons within our control".

Experts hope that that initiatives such as CEPI could provide a model for vaccine development that can coordinate between different research funders, establish clear and transparent processes for priority setting, establish standards for risk and benefit sharing, and generally inspire wider efforts to mobilise and deploy resources. At the international and governmental levels, this would require more long-term funding. Some argue that this could come through mechanisms that already exist, such as taxation and research budgets, with contributions adjusted to account for the projected benefits, population size and per capita income [7]. However, coordinating commitments such as mandatory contributions from World Health Organization (WHO) members to drive the research and development of health technologies relevant for disease outbreaks have proven difficult because of lack of broad support from governments.

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On the other hand, there have been signs of progress. The WHO, for instance, have recently looked to build standards for open data sharing and to better guide the collective research efforts of industry and government in emergencies. And there have been a number of other important initiatives, such as the Global Alliance for Vaccines and Immunization's (GAVI) use of advance market commitments in the development and production of new vaccines. The mechanism provides more incentives for industry to develop vaccines for smaller markets, by agreeing to purchase a certain volume even before it has been approved. It has proven particularly successful in the development of

new vaccines against pneumonia—the most deadly childhood disease on the planet.

In essence, experts believe there is a need to create conditions for more innovation while at the same time reducing the risk and uncertainties that have plagued vaccine development in the past. For emergency outbreak situations, this means developing clinical protocols that can be adapted depending on the nature of an outbreak, including regulatory requirements, import/export licences and networks of laboratories [7]. For creating a sustainable vaccine market, experts recommend mechanisms such as price and volume commitments as well as fresh approaches that can help companies to plan and reduce risk. "We need new ways of paying for innovation", Røttingen commented. "We need to separate the market of innovation and delivering a vaccine that gets market approval". This involves not just paying for an end product when it is used, but instead developing "innovation contracts" that directly reward innovation. "That is hard", he continued. "It is almost unseen in biomedical innovation at the moment".

One way forward, Røttingen, Hoyt and others suggest, is to heed lessons from the use of public–private partnership in sectors such as defence and aerospace, and historical successes in vaccine development. The US Biomedical Advanced Research and Development Authority (BARDA), for example, works with contractors in industry and academia and provides technical, operational and managerial support as well as core services to support product development and prepare for emergencies [3]. And an alliance between companies and the US military has boosted vaccine development in the past, before a series of legal, political and economic transformations in the 1970s and 1980s disrupted this partnership. "The military recognised that infectious disease was as big an enemy as they would ever come up against during the course of battle", Hoyt said. "Take the influenza vaccine for instance—all the basic science existed but we did not have the oversight of everything. They put together a commission that did that and a licenced flu vaccine was developed in just two years. There was so much situational awareness, they had the whole picture and could make really efficient go/no-go decisions. It was a different culture and a different time. There was a duty-driven approach to vaccine development—what that meant was industry was willing to work with military to develop vaccines that did not have much commercial value".

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The hope now is that the positive momentum in the wake of the Ebola outbreak could create a snowball effect to improve the funding and organisation of vaccine development and drive a return to a public service ethos in vaccine development. "Ebola showed that industry still has capacity to partner for the greater good—even when the business case is not strong", Hoyt said. "There is a need for better governance to mobilise that: partnerships that can make things more predictable and less painful that they were for Ebola. Clear communication of development priorities will make the process work better". The road ahead is likely to be long and arduous, but new financial models and technologies provide an opportunity to direct research and development in a manner that brings together companies, government, foundations and institutes to better prepare the world for the next epidemic—and to begin to address the long list of vaccine-preventable diseases we have failed up until now.

"The future of vaccine development is bright", Plotkin concluded. "On the one hand, we have new technologies that are developing, on the other hand we have new industry in developing countries and we have funders who can significantly help vaccine development to reach the end point of a licenced vaccine or stockpile for emergency use. I am relatively optimistic about the future".

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